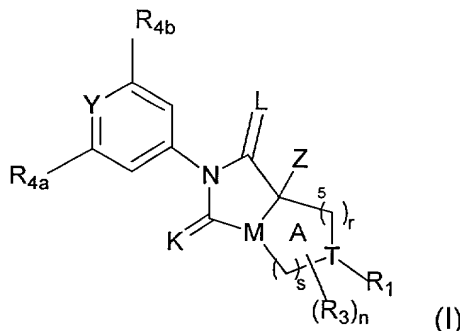


CLAIMS

We claim:

1. A compound having the formula (I),



- 5 or a pharmaceutically-acceptable salt thereof, in which:

L and K, taken independently, are O or S;

M is N or CH;

Y is CH or N;

- 10 Z is hydrogen, alkyl, or substituted alkyl, provided that Z may be selected from arylalkyl and heteroarylalkyl only when M is CH and/or when A has a second ring fused thereto;

T is nitrogen, CH, or a carbon atom substituted with an R₃ group;

- 15 R₁ is Q-aryl or Q-heteroaryl, wherein (a) when T is not nitrogen, Q is selected from a bond, -O-, -NR₁₀-, -S-, -C(=O)-, -CO₂-, -OC(=O)-, -NR₁₀C(=O)-, -C(=O)NR₁₀-, -NR₁₀CO₂-, C₁₋₄alkylene, C₁₋₄substituted alkylene, C₁₋₄alkenylene, C₁₋₄substituted alkenylene, and optionally-substituted bivalent C₁₋₄alkoxy, C₁₋₄alkylthio, C₁₋₄alkylamino, C₁₋₄aminoalkyl, C₀₋₄alkylsulfonyl, C₀₋₄alkylsulfonamide, C₁₋₄acyl, or C₁₋₄alkoxycarbonyl, or when Z is arylalkyl or heteroarylalkyl, R₁ may join with an R₃ group to form a fused carbocyclic or
- 20 heterocyclic ring; or (b) when T is nitrogen, then Q is selected from a bond, -C(=O)-, -CO₂-, -OC(=O)-, -C₁₋₄alkylene, C₁₋₄substituted alkylene, C₁₋₄alkenylene, C₁₋₄substituted alkenylene, or optionally-substituted bivalent C₁₋₄alkoxy, C₁₋₄alkylthio, C₁₋₄aminoalkyl, C₀₋₄alkylsulfonyl, C₀₋₄alkylsulfonamide,

C_{1-4} acyl, or C_{0-4} alkoxycarbonyl, provided that when M is N, T is N, r is 1, and s is 2 such that ring A is piperazine, R_1 is not an amine-protecting group;

R_3 is selected from (i) a substituent R_3 , wherein each substituent R_3 is individually attached to any available carbon or nitrogen atom of ring A and at each occurrence is selected independently of each other R_3 from halogen, alkyl, substituted alkyl, alkenyl, alkynyl, nitro, cyano, OR_8 , NR_8R_9 , CO_2R_8 , $(C=O)R_8$, $C(=O)NR_8R_9$, $NR_8C(=O)R_9$, $NR_8C(=O)OR_9$, $OC(=O)R_8$, $OC(=O)NR_8R_9$, SR_8 , $S(O)_qR_{8a}$, $NR_8SO_2R_9$, $SO_2NR_8R_9$, aryl, heteroaryl, heterocyclo, and cycloalkyl, and when attached to an atom of ring A other than T, R_3 is optionally keto ($=O$), provided that when R_3 is attached to the atom designated as the C-5 atom of ring A, then R_3 is not aryl or heteroaryl, and (ii) a first group R_3 and a second group R_3 , wherein the first group R_3 and the second group R_3 are attached to two adjacent atoms of ring A and together form an optionally-substituted carbocyclic or heterocyclic ring fused to ring A;

R_{4a} and R_{4b} are selected independently of each other from the group consisting of hydrogen, halogen, alkyl, substituted alkyl, alkenyl, alkynyl, nitro, cyano, hydroxy, alkoxy, substituted alkoxy, phenyloxy, benzyloxy, CO_2H , $C(=O)H$, amino, alkylamino, substituted alkylamino, CO_2 alkyl, $(C=O)$ alkyl, and alkylthio;

R_8 and R_9 (i) selected independently of each other are hydrogen, alkyl, substituted alkyl, alkenyl, alkynyl, alkoxy, cycloalkyl, aryl, heteroaryl, or heterocyclo; or (ii) taken together form a heterocyclo ring;

R_{8a} is alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclo;

R_{10} is hydrogen, alkyl, or substituted alkyl;

n is 0, 1, or 2;

q is 1, 2, or 3;

r is 1 or 2; and

s is 0, 1, or 2.

2. The compound of claim 1, or a pharmaceutically-acceptable salt thereof, wherein:

5 at least one of L and K is O;

Y is CH;

Z is hydrogen, lower alkyl, or lower alkyl substituted with hydroxy, alkoxy, halogen, cyano, nitro, amino, or alkylamino;

10 T is nitrogen, CH, or CR_{3a} wherein R_{3a} is hydroxy, amino, alkylamino, halogen, cyano, or C₁₋₄ alkyl optionally substituted with hydroxy, amino, alkylamino, halogen, or cyano;

R₁ is Q-aryl or Q-heteroaryl, wherein (a) when T is not nitrogen, Q is selected from a bond -O-, -NR₁₀-, -S-, -C(=O)-, -CO₂-, -OC(=O), C₁₋₄alkylene, C₁₋₄substituted alkylene, C₁₋₄alkenylene, C₁₋₄substituted alkenylene, or
15 optionally-substituted bivalent C₁₋₄alkoxy, C₁₋₄alkylthio, C₁₋₄alkylamino, C₁₋₄aminoalkyl, C₀₋₄alkylsulfonyl, C₀₋₄alkylsulfonamide, C₁₋₄acyl, and C₀₋₄alkoxycarbonyl; or (b) when T is nitrogen, then Q is selected from a bond, -C(=O)-, -CO₂-, -OC(=O), -C₁₋₄alkylene, C₁₋₄substituted alkylene, C₁₋₄alkenylene, and C₁₋₄substituted alkenylene;

20 R₃ is attached to any available carbon atom of ring A other than T and is selected from halogen, alkyl, substituted alkyl, alkenyl, alkynyl, nitro, cyano, OR₈, NR₈R₉, CO₂R₈, (C=O)R₈, C(=O)NR₈R₉, NR₈C(=O)R₉, NR₈C(=O)OR₉, OC(=O)R₈, OC(=O)NR₈R₉, SR₈, S(O)_qR_{8a}, NR₈SO₂R₉, SO₂NR₈R₉, aryl, heteroaryl, heterocyclo, cycloalkyl, and keto (=O), provided
25 that when R₃ is attached to the atom designated as the C-5 atom of ring A, then R₃ is not aryl or heteroaryl;

R_{4a} and R_{4b} are selected independently of each other from the group consisting of hydrogen, halogen, alkyl, alkoxy, cyano, nitro, haloalkyl, and haloalkoxy;

R_8 and R_9 selected independently of each other are hydrogen or alkyl,
5 and R_{8a} is alkyl;

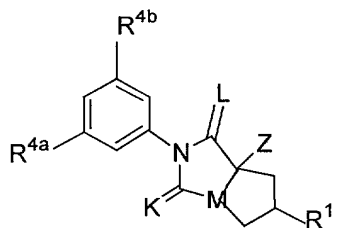
R_{10} is hydrogen, lower alkyl, or lower alkyl substituted with CO_2H or CO_2alkyl ;

n is 0 or 1;

r is 1; and

10 s is 1 or 2.

3. A compound according to claim 1 having the formula:

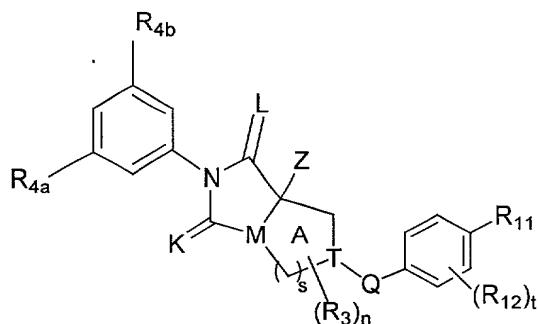


or a pharmaceutically-acceptable salt thereof.

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4. A compound according to claim 1, or a pharmaceutically-acceptable salt thereof, in which R_1 is $-\text{O}-\text{C}_{0-2}\text{alkylene-phenyl}$, $-\text{S}-\text{C}_{0-2}\text{alkylene-phenyl}$, $-\text{NR}_{10}-\text{C}_{0-2}\text{alkylene-phenyl}$, $-\text{C}_{1-3}\text{acyl-phenyl}$, $-\text{C}_{0-2}\text{alkoxycarbonyl-phenyl}$, or $-\text{NR}_{10}-\text{SO}_2\text{-phenyl}$, and said R_1 phenyl group has zero to two
20 substituents selected from halogen, $\text{C}_{1-4}\text{alkyl}$, nitro, cyano, hydroxy, $\text{C}_{1-4}\text{alkoxy}$, haloalkyl, haloalkoxy, CO_2H , C(=O)H , amino, $\text{C}_{1-4}\text{alkylamino}$, $\text{CO}_2\text{C}_{1-4}\text{alkyl}$, $\text{(C=O)C}_{1-4}\text{alkyl}$, $\text{C}_{1-4}\text{alkylthio}$, phenyl, phenyloxy, benzyl, or benzyloxy.

5. A compound according to claim 1, having the formula,



or a pharmaceutically-acceptable salt thereof, wherein:

- 5 Z is hydrogen, alkyl, or alkyl substituted with hydroxy, alkoxy, halogen, cyano, nitro, amino, or alkylamino;

R₁₁ is hydrogen, halogen, alkyl, alkoxy, haloalkyl, haloalkoxy, nitro, or cyano;

- 10 R₃ and R₁₂ are independently selected from alkyl, substituted alkyl, halogen, haloalkyl, haloalkoxy, nitro, cyano, hydroxy, alkoxy, amino, alkylamino, acyl, alkoxycarbonyl, carbamyl, sulfonyl, and sulfonamide;

n is 0 or 1;

s is 1 or 2; and

t is 0, 1, or 2.

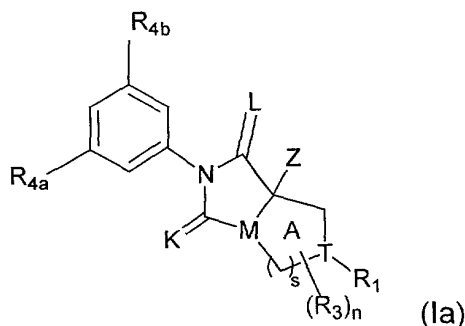
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6. The compound of claim 1, or a pharmaceutically-acceptable salt thereof, in which R_{4a} and R_{4b} are both halogen.

7. The compound of claim 1, or a pharmaceutically-acceptable salt
20 thereof, in which M is CH.

8. The compound of claim 1, or a pharmaceutically-acceptable salt thereof, wherein M is N, T is N, *r* is 1 and *s* is 2 such that ring A is piperazine, and R₁ is Q-aryl or Q-heteroaryl wherein Q is selected from a bond, -C(=O)-, -CO₂-, -OC(=O)-, -C₁₋₄alkylene, C₁₋₄substituted alkylene, C₁₋₄alkenylene, and C₁₋₄substituted alkenylene, provided that Q-R₁ is not benzyl or carbobenzyloxy.

9. A compound having the formula (Ia),



- 10 or a pharmaceutically-acceptable salt thereof, in which:

L and K are O or S;

M is N or CH;

- Z is hydrogen, alkyl, alkyl substituted with hydroxy, halogen, cyano, amino, or alkylamino; or when R₁ together with an R₃ group join to form a benzo ring fused to ring A, Z is arylalkyl or heteroarylalkyl;

T is nitrogen or CR₅;

R₁ is (a) -W-(CH₂)_m-Ar, or (b) taken together with an R₃ group to form a benzo ring fused to ring A, in which case Z is arylalkyl or heteroarylalkyl;

- Ar is aryl or heteroaryl substituted with zero or one R₁₁ and zero to two R₁₂ groups;

W is selected from (a) when T is CR₅, a bond, -O-, -NR₁₀-, -S-, -C(=O)-, -CO₂-, and -CH(R₁₃)-C(=O)-; and (b) when T is nitrogen, a bond, -C(=O)-, -

CO₂-, and -CH(R₁₃)-C(=O)-, provided that when M is N, T is N, and s is 2 such that ring A is piperazine, then W-(CH₂)_m-Ar is not benzyl or carbobenzyloxy;

R₃ is selected from (i) a substituent R₃, wherein each substituent R₃ is individually attached to any available carbon or nitrogen atom of ring A and at each occurrence is selected independently of each other R₃ from halogen, alkyl, substituted alkyl, alkenyl, nitro, cyano, keto (=O), OR₈, NR₈R₉, CO₂R₈, (C=O)R₈, C(=O)NR₈R₉, NR₈C(=O)R₉, NR₈C(=O)OR₉, OC(=O)R₈, OC(=O)NR₈R₉, SR₈, S(O)_qR_{8a}, NR₈SO₂R₉, SO₂NR₈R₉, aryl, heteroaryl, heterocyclo, and cycloalkyl; and (ii) a first group R₃ and a second group R₃, wherein the first group R₃ and the second group R₃ are attached to two adjacent atoms of ring A and together form an optionally-substituted carbocyclic or heterocyclic ring fused to ring A, or one R₃ together with R₁ may join to form a fused benzo ring;

R₅ is hydrogen, halogen, alkyl, alkenyl, hydroxy, nitro, cyano, hydroxy, alkoxy, amino, or alkylamino, or C₁₋₄ alkyl optionally substituted with hydroxy, amino, alkylamino, halogen, or cyano;

R_{4a} and R_{4b} are selected independently of each other from the group consisting of hydrogen, halogen, alkyl, nitro, cyano, haloalkyl, and haloalkoxy;

R₈ and R₉ (i) selected independently of each other are hydrogen, alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclo; or (ii) taken together form a heterocyclo ring;

R_{8a} is alkyl, substituted alkyl, cycloalkyl, aryl, heteroaryl, or heterocyclo;

R₁₁ is hydrogen, halogen, alkyl, hydroxy, alkoxy, amino, alkylamino, haloalkyl, haloalkoxy, nitro, or cyano;

R₁₂ is alkyl, substituted alkyl, halogen, haloalkyl, haloalkoxy, nitro, cyano, hydroxy, alkoxy, substituted alkoxy, amino, alkylamino, acyl, alkoxycarbonyl, carbamyl, sulfonyl, or sulfonamide;

R₁₀ and R₁₃ are independently hydrogen, alkyl, or substituted alkyl;

m is 0, 1, 2, 3, or 4;

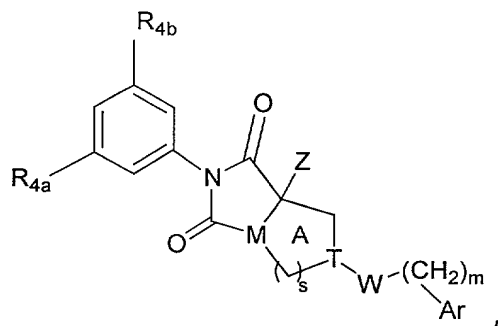
n is 0, 1 or 2;

q is 1, 2, or 3; and

s is 1 or 2.

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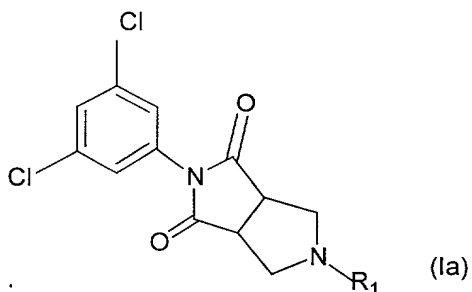
10. A compound according to claim 9, having the formula:



or a pharmaceutically-acceptable salt thereof.

10 11. A compound according to claim 10, in which Ar is optionally substituted phenyl or isoquinolinyl and R_{4a} and R_{4b} are both halogen.

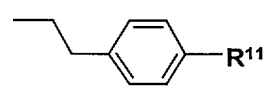
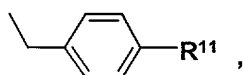
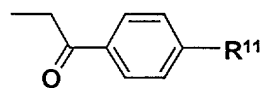
12. A compound according to claim 9 having the formula (Ia),



15

in which

R_1 is selected from

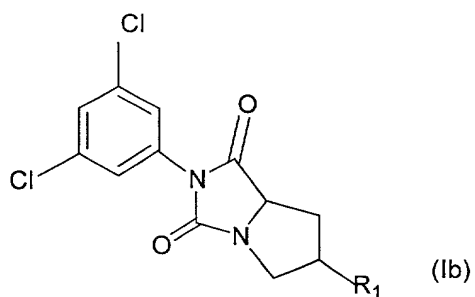


and

R_{11} is selected from hydrogen, bromo, chloro, cyano, and methoxy.

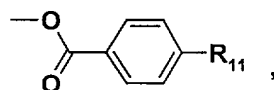
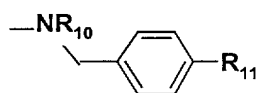
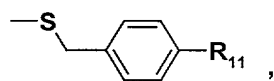
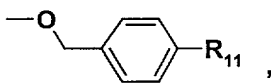
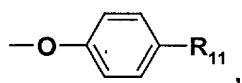
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13. A compound according to claim 9 having the formula (Ib),



in which R_1 is selected from:

10



;

R_{11} is selected from hydrogen, bromo, chloro, cyano, and methoxy, and R_{10} is selected from hydrogen and alkyl.

15

14. A compound according to claim 9 which is: (I)
- (7aS,6S)-2-(3,5-dichloro-phenyl)-6-(4-bromophenoxy)-tetrahydro-pyrrolo[1,2-c]imidazole-1,3-dione;
- (7aS,6S)-2-(3,5-dichloro-phenyl)-6-(4-bromophenoxy)-tetrahydro-pyrrolo[1,2-c]imidazole-1,3-dione;
- 5 5-[2-(4-Chlorophenyl)ethyl]-2-(3,5-dichlorophenyl)tetrahydropyrrolo[3,4-c]pyrrole-1,3(2H,3aH)-dione;
- 7-[2-(4-Bromophenyl)ethyl]-2-(3,5-dichlorophenyl)-tetrahydro-imidazo[1,5-a]pyrazine-1,3-dione;
- 10 7-[2-(4-Bromophenyl)-1-methyl-2-oxo-ethyl]-2-(3,5-dichlorophenyl)-tetrahydro-imidazo[1,5-a]pyrazine-1,3-dione;
- (7aS,6S)-4-[[2-(3,5-dichloro-phenyl)-1,3-dioxo-hexahydro-pyrrolo[1,2-c]imidazol-6-ylamino]-methyl]-benzonitrile;
- (7aS,6S)-N-(4-cyano-benzyl)-N-[2-(3,5-dichloro-phenyl)-1,3-dioxo-hexahydro-pyrrolo[1,2-c]imidazol-6-yl]-acetamide;
- 15 (6R,7aS)-[6-(4-bromobenzyloxy)-2-(3,5-dichlorophenyl)-1,3-dioxo-tetrahydro-pyrrolo[1,2-c]imidazol-7a-yl]-acetic acid methyl ester;
- 5-[2-(4-Bromophenyl)-2-oxoethyl]-2-(3,5-dichlorophenyl)-tetrahydropyrrolo[3,4-c]pyrrole-1,3-dione;
- 20 2-(3,5-Dichlorophenyl)-5-naphthalen-2-ylmethyl-tetrahydropyrrolo[3,4-c]pyrrole-1,3-dione;
- (7aS,6S)-2-(3,5-dichloro-phenyl)-6-(4-bromobenzoyloxy)-tetrahydro-pyrrolo[1,2-c]imidazole-1,3-dione;
- 10a-(4-Bromo-benzyl)-2-(3,5-dichloro-phenyl)-10,10a-dihydro-5H-imidazo[1,5-b]isoquinoline-1,3-dione;
- 25 (6S,7aS)-6-(4-bromobenzyloxy)-2-(3,5-dichlorophenyl)-tetrahydro-pyrrolo[1,2-c]imidazole-1,3-dione; or (ii) a pharmaceutically-acceptable salt thereof.

15. A pharmaceutical composition for treating an inflammatory or immune disease comprising (a) at least one compound according to claim 1, or a pharmaceutically acceptable salt thereof, and (b) a pharmaceutically acceptable carrier or diluent.

16. A pharmaceutical composition for treating an inflammatory or immune disease comprising (a) at least one compound according to claim 9, or a pharmaceutically acceptable salt thereof, and (b) a pharmaceutically acceptable carrier or diluent.

17. A pharmaceutical composition comprising (i) at least one compound of claim 1 or a pharmaceutically acceptable salt thereof; (ii) one or more second compositions effective for treating an inflammatory or immune disease; and (iii) a pharmaceutically-acceptable carrier.

18. A method of treating an inflammatory or immune disease comprising administering to a mammal in need of such treatment a therapeutically-effective amount of a composition according to claim 15.

20

19. A method of inhibiting a Leukointegrin/ICAM-associated condition which comprises administering to a patient in need thereof an effective amount of a compound of claim 1.

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